PERIODICAL

PUBLIC LIBRARY
MAR 28 1947
DETROIT

American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Mr. James L. Rogers, President, American Pharmaceutical Manufacturers' Association

Since 1825 *January 1947*

R v. 119 1947

Through Education in

SCIENCE.....

FOUNDED
1821

THE increasing opportunities in Pharmacy, in Chemistry, in Bacteriology, and in Biology are made available to the men and women who have undertaken this necessary formal preparation. This College offers B. Sc. degree courses in each of these four fields. Selected Graduate Studies are available. Terms commence each September. Write for catalog.

Philadelphia College of Pharmacy and Science
43d St., Woodland and Kingsessing Aves.
Philadelphia 4, Pa.

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription, $3.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 30 Cents — Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879

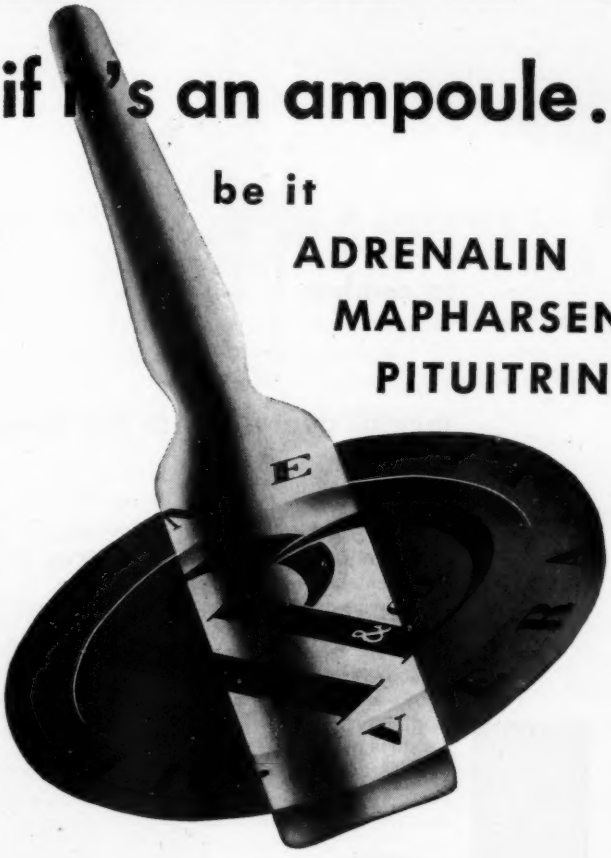
Rlf

ADRENALIN IN OIL
ADRENALIN SOLUTION
ADREPHINE
ADROCAINE
AMYL NITRITE
ASCORBIC ACID
BISMUTH SALICYLATE IN OIL
CALCIUM CHLORIDE
CALCIUM GLUCONATE
CAMPHOR IN OIL
CHAULMOOGRA OIL
DEXTROSE, U.S.P.
DICHLOR-MAPHARSEN
DIGIFORTIS
DIGITALONE
DISTILLED WATER
EPHEDRINE SULFATE
ERGONE
ERGOT ASEPTIC
ETALATE
HEXAVIBEX
HISTAMINE PHOSPHATE
IRON ARSENITE
IRON CACODYLATE
IRON CITRATE, GREEN
LIPO-BISMOL
LIPO-LUTIN

LIVER EXTRACT MAPHARSEN MORPHINE AND ATROPINE PITRESSIN
MAGNESIUM SULFATE MERCURY SUCCINIMIDE PITOCIN PITUITRIN

if it's an ampoule..

be it
ADRENALIN
MAPHARSEN
PITUITRIN..



•• or any one of more than a hundred other preparations, sealed in glass with unquestioned sterility and in accurate dosage, you are assured the finest ingredients in their most stable and therapeutically efficacious forms. The extensive PARKE-DAVIS ampoule line affords physician and pharmacist a wide selection of important medicinal preparations. It is "as good pharmacy to stock and dispense them as it is good medicine to prescribe them."

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

to combat

mental depression in the menopause

"... because the involutional period is fraught with sadness the different forms of mental disorder of this age may be highly colored with mental depression."*

Severe menopausal depression, marked by apathy and psychomotor retardation, is frequently progressive. Hence, if not promptly and effectively treated, it may seriously impair the patient's normal capacity for useful living.

In such cases, Benzedrine Sulfate helps to overcome the depression, to restore optimism and to reawaken the savor and zest of life. Needless to say, Benzedrine Sulfate is not indicated in the casual case of low spirits, as distinguished from true prolonged mental depression.

*Hinsie, Leland E.: The Person in the Body, an Introduction to Psychosomatic Medicine, New York, W. W. Norton & Co., 1945, p. 223.

Tablets and Elixir

benzedrine sulfate

(racemic amphetamine sulfate, S.K.F.)

Smith, Kline & French Laboratories, *Philadelphia, Pa.*

two weeks for an answer

When the diagnosis of male climacteric is suspected but not definitely proved, a therapeutic test with ORETON (testosterone propionate) will provide the answer in two weeks. If androgen deficiency is the cause of symptoms, they will be alleviated by intramuscular injections of male sex hormone as ORETON 25 mg. daily for 5 days weekly over a two weeks period. Subsequently, manifestations of the male climacteric may be controlled with the same dosage injected two or three times weekly, and eventually equilibrium can be maintained with ORETON-M (methyltestosterone) Tablets.

ORETON

ORETON (testosterone propionate in oil), for intramuscular injection, in ampules of 1 cc. containing 5, 10 and 25 mg., in boxes of 3, 6 and 50. Multiple dose vials of 10 cc., 25 mg. per cc. Box of 1 vial. ORETON-M (methyltestosterone) Tablets 10 mg., in boxes of 15, 30 and 100.

Trade-Marks ORETON and ORETON-M—
Reg. U. S. Pat. Off.

SCHERING

Schering CORPORATION • BLOOMFIELD, N. J.

IN CANADA, SCHERING CORP. LTD., MONTREAL

CREAMALIN

TRADEMARK REG. U. S. PAT. OFF. & CANADA

BRAND OF ALUMINUM HYDROXIDE GEL

TABLETS

NEW

P. O. S. PACKAGE

(Point of Sale)

Attractive Counter Display Carton takes little space.

(Holds 12 tins of 12 tablets)

- Post-war flat tin of 12 tablets
- Convenient for pocket or purse
- Display unit for counter

The many patients who have used CREAMALIN TABLETS will welcome the new P. O. S. (point of sale) post-war flat tin of 12. The convenient tin may be carried readily in the vest pocket or purse, with assurance that the tablets will not be broken.

As a progressive pharmacist, you will gain added sales by placing the small but attractive counter display near your cash register—the point of sale.

other **CREAMALIN** *forms*

CREAMALIN is available in a variety of dosage forms to meet individual desires. These are as follows:

Creamalin Liquid—(flavored, highly flavored and unflavored)
Creamalin with Mineral Oil
Creamalin Tablets
Creamalin Capsules

A generous Introductory Offer is presented to all druggists
Ask your wholesaler or your Winthrop representative for details.

Winthrop CHEMICAL COMPANY, INC.

Complete WINTHROP CATALOG in American Druggist Blue Book and Drug Topics Red Book

Pharmaceuticals of merit for the physician 170 VARICK STREET NEW YORK 13, N. Y.

AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

LINWOOD F. TICE, Ph. G., B. Sc., M. Sc., Editor

Austin A. Dodge, Ph. C., B. Sc., Ph. D., Assistant to the Editor

John E. Kramer, B. Sc., Business Manager

COMMITTEE ON PUBLICATION

E. Fullerton Cook, P. D., Ph. M., M. S., Chairman

Mitchell Bernstein, P. D., M. D., F. A. C. P.

Louis Gershenfeld, P. D., Ph. M., D. Sc.

Marin S. Dunn, A. M., Ph. D.

John K. Thum, Ph. G., Ph. M.

J. W. Sturmer, Phar. D., Ph. M., D. Sc., Secretary

Ivor Griffith, P. D., Ph. M., D. Sc., F. R. S. A., ex officio

Vol. 119. JANUARY, 1947 No. 1

CONTENTS

Editorial:

Drug Manufacture and the Medical Profession 2

Articles:

Progress in Fungous Disease Therapy. By Louis Schwartz, M. D. 5

Progress in Allergy Therapy. By Samuel M. Feinberg, M. D. 15

The General Medical Aspects of Atomic Energy. By Frank H. Krusen, M. D. 24

Selected Abstracts 35

Book Reviews 41

E D I T O R I A L

DRUG MANUFACTURE AND THE MEDICAL PROFESSION

THIS issue of the journal contains three articles selected from the several excellent papers presented at the recent meeting of the American Pharmaceutical Manufacturers' Association.

Recent years have witnessed a constant growth in harmony and cordial relations between the medical profession and those manufacturing drug products. This speaks well not only for the two groups involved but also for the welfare of pharmacy and the public at large. It might be of interest to examine some of the factors responsible for this growth of mutual respect since one's concern and regard for the other has not always been so commendable.

At one time physicians in their treatment of patients having many diseases relied largely on nature, psychiatry (then known as a good bedside manner) and God. The drugs used were for the most part palliatives, useful in keeping the patient comfortable and satisfied until the disease either ran its course or the patient succumbed. Most diseases then were treated as today one treats the common cold, for which there still is no specific.

Pharmaceutical manufacture consisted of making either preparations for use by the physician or almost identical "remedies" for direct sale to the sick for self-treatment. In many cases the patient received the same preparation whether he went to a physician, a quack, or his corner druggist and his chances of cure were none too good in any event. Physicians knew this but rarely admitted it, the manufacturer while professing to be strictly "ethical" was not and the public, as usual, was simply confused.

Slowly but surely a new trend developed largely due to the advent of highly specific drugs; drugs which were not palliatives but potent substances either attacking an invading organism or correcting a certain physiologic deficiency and thus remedying the diseased state. Nature no longer needed to be the sole source of hope, and diseases formerly meaning certain death gave way to the growing list

of specifics. The inadvisability of self-medication now was greatly increased since it involved greater risk of damage as well as postponement of proper diagnosis and treatment. This trend was finally crystallized in the provisions of the Food, Drug and Cosmetic Act which established a sound basis for the relationship of manufacturer, pharmacist, patient and physician.

Pharmaceutical manufacturers saw the death of the patent medicine era and most agreed it had come to a timely end. The new day envisioned closer cooperation with the medical profession since now each was quite dependent upon the other. The physician could no longer practice medicine without the new specifics manufactured on a production basis in the large laboratories; the manufacturer could sell most of these specifics only to physicians or on their prescription and each new product needed to be clinically tested before it could be sold at all.

Another effect of this new interdependence was the removal of barriers between the two groups. Physicians became employees of drug manufacturers to help solve their problems in arranging clinical trials, establishing regimens of treatment, serving on research teams etc., and practicing physicians looked with new respect on detailing pharmacists who now often helped them solve difficult clinical problems and save patients' lives. All this has led to better understanding and teamwork between the two groups.

The next step in the picture is already clear to those who see pharmacy in broad perspective. Retail pharmacy, insofar as its professional aspects is concerned, is undergoing a marked change. In some respects this change is difficult since the retail pharmacist is involved in both commercial as well as professional activities. Although both are public services, it is his professional status that sets him apart from other commercial enterprises and therefore it is the professional that must be maintained at all costs. With the increasing use of specifics and the decrease in compounding skill required, pharmacists must fill a new place in their service to physicians. In addition to filling prescriptions, many of which will be simple, they must work more closely with the physician than ever before. It is the practicing pharmacist who now has a golden opportunity to help the physician in the selection and use of new drugs. If he does this the picture will then be complete from manufacture to use—the manufacturer, the physician, and the pharmacist. Manufacturers have already firmly

established themselves as indispensable servants of public health; the physician's place has never been in doubt; pharmacists now must meet their challenge if the team is to be complete. Many promising signs augur well for the continued existence of our profession.

L. F. TICE

PROGRESS IN FUNGOUS DISEASE THERAPY*

By Louis Schwartz, M. D.**

AS early as 1677, fungi were discovered as causing the yellow spots on roses. In 1839, Langenback demonstrated the organism causing thrush (*Oidium albicans*), and Schoenlein, the organism causing favus (*Acherion schoenleini*). Descriptions of the fungi causing tinea circinata and tinea versicolor followed in 1842 and 1846. In 1870, Tilbury Fox described tinea pedis (1).

Interest in the fungous diseases of man declined from that time until early in this century, when Sabouraud, Castellani, Jadassohn, and Bloch in Europe, and Williams, Weidman, Hopkins, Sulzberger, Peck, and Lewis in America, among others, revived interest in the subject.

Treatment of the superficial fungous infections, even as early as 1880, consisted of topical applications of the then known parasiticides and the internal administration of tonics. Duhring, in 1883 (2), used mercurials, creosote, sulfur, phenol, and iodine to kill the fungi. He recognized acute and chronic, as well as resistant, types of fungous diseases, and stated that the extent, site, and degree of the inflammatory reaction should govern the therapy to be used.

In estimating the progress made in fungous disease therapy, I shall review the literature, beginning with the treatment used 30 years ago as described by the authors of standard texts, but I shall consider only the treatment of tinea pedis and tinea capitis.

Tinea pedis

Schamberg, in 1917 (3), used ointments and lotions. The types selected depended on the clinical signs. He advocated careful cleansing of the affected parts, manual removal of dead skin, and wet dressings to allay inflammation. As fungicides, he used dilute tincture of iodine betanaphthol, resorcin, tar, ammoniated mercury and chrysarobin. As keratolytics he used Whitfield's ointment and Drew's ointment.

Sutton, in 1927 (4), stated that Strickler, Engman, and McGarry had used fungous vaccine therapy (trichophytin) with success.

* Presented at the Midyear Meeting of the American Pharmaceutical Manufacturers' Association, December 9, 1946.

** Medical Director; Chief, Office of Dermatology, Industrial Hygiene Division, U. S. Public Health Service.

Sutton said that Whitfield's ointment was thought to be a specific for tinea pedis, "but now we know that such is not the case." To remove dead skin, he mentioned mechanical debridement. He stated that the plan of the treatment must be individualized. In acutely inflammatory cases, soothing remedies such as "lead and opium or Burow's solution may be tried." He warned against the use of irritating remedies. In addition to topical applications indicated by Schamberg in 1917, Sutton mentioned the use of mercurochrome, methylene blue, picric acid, and potassium permanganate.

Investigations of the fungicidal properties of various chemicals were carried on in the period 1930-1938. Woodward, *et al* (5), found that the introduction of halgolen atoms into dihydric phenols increased their fungicidal powers. They also found that the fungicidal powers of iodine, hexylresorcinol, and chlorothymol were greatly reduced in the presence of serum, and that benzoic acid, salicylic acid, and sodium thiosulfate were entirely ineffective in protein suspensions.

In 1938, Peck and Rosenfeld (6) called attention to the fungicidal powers of the fatty acids and their normal salts contained in sweat. They stated that the normal salts, as a rule, were less effective than the acids, with the exception of sodium propionate and sodium undecylenate, and that the acids with an odd number of carbon atoms were more fungicidal than those with an even number. They stated that valeric acid with 5 carbon atoms was the most powerful, but that pelargonic acid with 9 carbon atoms was almost as strong a fungicide. In 1939, Peck, *et al* (7), stated that the fungicidal properties of sweat were due to its content of acetic, propionic, caproic, caprylic, lactic, and ascorbic acids. These publications were the bases for the present interest in therapy with the salts of fatty acids.

In 1939, Lewis and Hopper (1) published "An Introduction to Medical Mycology". In this book they divide the treatment of tinea pedis into 2 classes: topical applications and desensitization. In the acute inflammatory stage of the disease they advocate wet dressings of Burow's solution, (1-15) boric acid, potassium permanganate 1:3000, tannic acid 2 per cent, aqueous solution of gentian violet 1 per cent, and aqueous solution of malachite green 1 per cent. They recommend the incision of large vesisicles and blebs. They state that keratolytics are useful in peeling the stratum corneum, which contains the fungi, and also in preparing the way for fungicides to act. Salicylic acid and resorcinol are named as keratolytics. They list a

number of fungicides, but no new ones. In their opinion, desensitization with trichophytin and the implantation of *B. subtilis,* strains of *Penicillium* and *Aspergillus* have not met with success.

They state that the patient should be treated as an individual. The drug used should depend on personal requirements, such as the type of fungus, the degree of sensitization, and the clinical symptoms. They believe that the cure of chronic dermatophytosis is rarely achieved and that recurrences are more common than reinfections.

At the beginning of World War II, the finding of a large percentage of soldiers and industrial workers affected with tinea pedis caused a revival of research into the treatment and prevention of this troublesome disease. Many new fungicidal remedies and new methods of prevention were advocated.

J. Gardner Hopkins was appointed to study fungous infections in the Army. The U. S. Public Health Service made studies of dermatophytosis among industrial workers (7a).

In 1943, Peck and Schwartz gave formulae for the treatment of superficial fungous infections. Some of these are sodium propionate, sodium pentachlorphenate, and oxyquinoline sulfate.

Keeney and his associates (8, 9, 10, 11) reported in 1943 that sodium propionate, although not fungicidal, appeared to be effective in the treatment of tinea pedis, tinea cruris, tinea capitis, thrush, otomycosis, and black tongue. In 1944, he stated that sodium caprylate, sodium caprate, and sodium undecylenate were more fungistatic than the propionates, valerates, and caproates. As the fatty acid chain lengthened, he said, fungicidal properties increased. Later in 1944, before the National Research Council, Keeney recommended the use of sodium caprate as a treatment for tinea pedis rather than sodium propionate or undecylenate.

At the same meeting, J. Gardner Hopkins (12) stated that dinitrocyclohexylphenol 10 per cent was the best of the remedies he had tried. This was because it immediately stopped itching. He said that orthocyclohexylparachlorphenol 1:50,000, proposed by E. G. Klarmann, also was good. In testing a number of powders Dr. Hopkins found that those containing fungicidal agents were only slightly more efficacious than ordinary talcum.

In 1944, Dr. Hopkins reported to the National Research Council that, although he recommended undecylenic acid for dermatophytosis of the feet, he did not consider it an ideal preparation. But it is more

effective than most available preparations, he said, and is safe for men to use on their own initiative.

Peck, *et al* (7a), on examining 2,123 workers, found about 45 per cent infected with tinea pedis. They also found that shower room flooring is not a likely source of infection; that no reduction in the incidence of tinea pedis was shown by fungicidal foot baths after showers; and that dermatophytosis and its allergic manifestations were not an important cause of lost time among industrial workers.

Goldman, *et al* (13), stated that fungous diseases of the feet may improve spontaneously by rest in bed. The best topical treatment, he said, is phenylmercuric borate 1:500 with 1 per cent boric acid in vanishing cream.

Shapiro and Rothman (14), in 1945, stated that zinc undecylenate 20 per cent and undecylenic acid 5 per cent in a vanishing emulsion (a proprietary remedy) cured 86 per cent of the cases of tinea pedis and tinea cruris in 4 weeks. Relapses did not occur if the treatment was continued.

Hillegas and Camps (15) found Brilliant Green was 12½ times, and gentian violet 2½ times, more fungistatic than undecylenic acid; and sodium salt of 2-chloro-4-phenylphenol, 5 times more fungicidal than undecylenic acid.

In the treatment of tinea pedis, Schwartz and his associates at present are successfully using as fungicides both salicylanilide 5 per cent in Carbowax 1500 and saturated solution of copper undecylenate in Carbowax 1500.

In this review of the literature, what progress is indicated in the treatment of tinea pedis? Today there is less use of salicylic acid and other keratolytics which are not fungicidal and tend to inflame an already injured skin. It is preferable to employ manual removal of dead epithelium and to open the vesicles and blebs so as to enable the fungicide to act on the fungus.

A host of new, powerful, comparatively nonirritating fungicides have been added to our armamentarium. The efficacy of our ointment bases has been increased by the addition of the synthetic wetting agents which enable the fungicide to better attack the fungi.

Individual treatment, according to the needs and clinical symptoms of the patient, is stressed. One stereotyped remedy or form of treatment for all cases is no longer advocated. Inflamed skin caused

by fungous infection is now treated by soothing applications, and fungicides are applied only after the acute symptoms subside.

Notable among the many new fungicides are propionic and undecylenic acids, and their sodium, zinc, and copper salts; the chlorophenols, the bromcresols, the phenylphenols, the phenylmercuric salts, the organic zinc compounds, the organic copper compounds, such as copper naphthenate, copper pentachlorphenate, etc., and the quaternary ammonium compounds.

It is not difficult to clear up a case of tinea pedis by the judicious use of wet dressings and these modern fungicides. But as recurrences and reinfections often occur, prophylaxis is stressed. The patient is instructed in foot hygiene. He is told to keep the feet dry, especially the interdigital spaces; to manually remove dead epithelium, which is the breeding place of fungi; and to avoid walking barefooted in public bath houses. These preventive measures also should be practiced by people who are free from athlete's foot. Foot baths in public showers, fungicidal mats, sprays, and fungicidal flooring have been found of no value in the prevention of athlete's foot.

Tinea capitis

The treatment of tinea tonsurans advised by Duhring in 1883 (2) was manual epilation of diseased hairs and topical applications. He stated that sulfur, ammoniated mercury, creosote, phenol, mercuric nitrate, and iodine were used as fungicides. The chronic patches were painted once a week with glacial acetic acid or with cantharides in collodion and the above fungicides were applied daily. He knew that tinea tonsurans usually disappeared at puberty.

Corlett, in 1899 (16), advised segregation of infected children, or enveloping the scalp in impervious medicated dressings held in place by a skull cap. He stated that the hair should be clipped close or shaved and the diseased area should be manually epilated. He advised that the scalp should be cleansed daily with soap and water, dried, and benzine applied, followed by the parasiticide. As parasiticides, he used phenol 4-6 per cent, copper oleate 20 per cent, or mercuric oleate 20 per cent in vaseline. He also used formalin in 5-15 per cent solution.

Schamberg, in 1917 (3), stated that Sabouraud, in Paris, was able to cure tinea capitis with one X-ray treatment. Schamberg himself treated the disease by manual epilation of the diseased hairs and

the application of parasiticides. He used betanaphthol 12 per cent, tar 35-50 per cent, chrysarobin 4-7 per cent, phenol 5 per cent, and oil of cade. He stated that none of these medications is superior to another. It is the perseverance and the thoroughness in the use of the preparations that produce a successful result.

Darier, in 1920 (17), stressed that prophylaxis necessitates the immediate strict isolation of the patient. He treated tinea capitis by cutting the hair short every 8 to 10 days. He painted tincture of iodine over the entire scalp every day; and applied an occlusion dressing of iodized vaseline or chrysarobin ointment. He stated that where X-rays were available, epilation by means of X-ray was the method of choice.

Sutton, in 1927 (4), stated that combs, brushes, interchange of caps, and barber shops were the main sources of infection. He explained that the infected hairs must be removed so that antiseptics can attack the parasites in the bottom and sides of the hair follicle. He said that epilation is best done by X-rays, but that barium sulfide or frequent shaving of the head may be used. He did not consider justifiable the administration of thallium acetate to epilate the scalp, although it is at present the method of choice in Mexico City. He considered that iodine, ammoniated mercury, chrysarobin, sulfur, tar, and bethanaphthol were the best fungicides.

These authorities represented the most advanced thought on the subject up to the beginning of World War II.

In 1941, Livingood and Pillsbury (18) observed 105 cases of the non-inflammatory type of tinea capitis caused by *M. audouini,* and found that 27 per cent were cured spontaneously without treatment in from 3 months to 2 years. As fungicides, they used tincture of iodine, with and without 2 per cent aerosols, iodine ointments with wetting-agent bases, phenylmercuric nitrate, ammoniated mercury, sulfur, and salicylic acid. They noted no consistent good effect from any single type of these fungicides. And they recommended X-ray epilation when available.

In 1942, a rapid increase in the occurrence of ringworm of the scalp was noted, especially in large eastern cities. The epidemic spread. By 1943 reports came to the Public Health Service of epidemics in smaller cities as far west as the Mississippi River. This sudden outbreak, of course, stimulated renewed interest in the therapy of the disease and its epidemiology.

Poth and Kaliski (19) treated 15 cases of tinea capitis in 1942 with daily oral doses of 5000 I. U. of estrone and the daily application of an ointment containing 5000 I. U. per gram. They also treated 15 cases with daily oral doses of 75,000 I. U. of diethylstilbestrol and the application of an ointment containing 4000 I. U. per gram of this drug. They reported that all were cured except two patients who had discontinued treatment.

Keeney and Brayler (8) stated in 1943 that they used effectively sodium propionate in the treatment of tinea capitis.

In 1944, Schwartz, *et al,* of the U. S. Public Health Service, were requested to undertake an experiment in Hagerstown, Maryland, to find the method of spread, and formulate a method to control the epidemic that was present in that city. They made a preliminary report in 1945 (20); the final report was published in 1946 (20a).

This epidemic consisted of more than 600 cases or about 10 per cent of the children in the city's grade school. It was controlled in one year by topical applications. This was done without barring infected children from school or other public places. No X-ray epilation was used. Two years after the experiment began, all the children were cured except 15 who refused treatment.

It was found that the electric clippers in barber shops were the chief sources of infection. Seventeen different topical applications were tried, including zinc undecylenate and undecylenic acid, sodium propionate and propionic acid, copper oleate, colloidal iodine, a number of quaternary ammonium compounds, pentachlorphenol, phenylmercuric salicylate, copper oleate, copper undecylenate, and salicylanilide. Copper undecylenate and salicylanilide in a base of Carbowax 1500 were the most efficacious remedies used. The children were treated daily in the schools by trained attendants who clipped the heads of infected children every 10 days.

McKee, *et al,* in 1946 (21), reported that by using trimethylcetyl-ammonium pentachlorphenate they cured 54 per cent of their cases, but stated that X-ray epilation was preferred.

Carrick reported in 1946 (22) that he cured 41 per cent of his patients with copper oleate, 40 per cent with zinc undecylenate and undecylenic acid, 59 per cent with sodium propionate and propionic acid, and all in about 130 days. But he stated that none of these ointments should be considered a substitute for X-ray epilation.

Lewis and Hopper (23) found that no treatment for tinea capitis caused by *M. audouini* offered as much promise of prompt cure as the regimen which includes X-ray epilation. In their textbook (7), they advocate manual epilation and application of 10 per cent ammoniated mercury for small patches, X-ray epilation, and 3 per cent ammoniated mercury for larger areas.

Miller, *et al* (24), tried dinitrocyclohexylphenol, sodium propionate, undecylenic acid, trinitrophenol, benzoic and salicylic acids, and iodine and mercury. But they effected no more than 12 per cent cures. They advocate topical therapy as an adjuvant to X-ray epilation.

Strickler reported 64 per cent of cures with a mixture containing:

Iodine	78
Red blood cells	2
Sodium Chloride	1.9
Chlorophyll	2
Deceresol	10
Magnesium Peroxide	8
Spleen extract	0.005

It can be seen from these reports that the treatment of tinea capitis has progressed. Cures are now attained by topical applications without X-ray epilation, or by administering thallium acetate. In order to attain a cure with topical applications, the treatment must be regular, frequent, and continuous over a period of several months. X-ray is a valuable therapeutic aid, but epilation without subsequent topical applications does not cure.

The cure by topical applications has been made possible by the introduction into medicine of powerful fungicides long used by industry as anti-mildew agents, synthetic detergents, and surface active agents; and by penetrants also used in industry for carrying dyes into textiles. The object of epilation, by whatever means, is to remove the infected hairs and leave the follicle open so that the fungicides can enter and destroy the fungi on the sides and bottom of the follicle and prevent infection of the new growing hairs.

Clipping the hair close to the scalp (and burning it) removes much of the infection and permits the fungicides to be applied thoroughly to the scalp. The ointment bases contain wetting agents (many of which are also fungicides), which enable the fungicides to

enter alongside the hair into the follicle and actually bring the fungicide in contact with the fungus. This obviates the need for epilation.

Children need not be kept out of school in order to prevent the spread of the disease. The original idea was to isolate infected children from non-infected children. This cannot be accomplished by excluding them from school because infected and noninfected children play together outside of school.

As the disease is spread by infected hairs, the following procedures are recommended: hair of infected children should be kept closely clipped; caps should be worn; barbers should be instructed to sterilize their implements after cutting the hair of each noninfected child, and not to cut the hair of known infected children. Mothers should be instructed to shampoo the child's head thoroughly after each haircut. By these measures, the chance of the infection spreading is greatly reduced. The need of keeping children from school will be nullified. Moreover, sending the infected children to school is advantageous because the school is a convenient place in which to treat the infected children every day, to check the progress of the disease, and to determine when a cure is effected.

REFERENCES

1. Lewis, George M., and Hopper, Mary E.: An Introduction to Medical Mycology, ed. 2, Chicago, Year Book Publishers, 1937.

2. Duhring, Louis A.: Diseases of the Skin, ed. 3, Philadelphia, J. B. Lippincott & Co., 1883, pp. 602-612.

3. Schamberg, Jay Frank: Diseases of the Skin and the Eruptive Fevers, ed. 3, Philadelphia and London, W. B. Saunders Company, 1917, pp. 181-185.

4. Sutton, Richard L.: Diseases of the Skin, ed. 7, St. Louis, The C. V. Mosby Co., 1928.

5. Woodward, G., Kingery, W., and Williams, R.: The Fungicidal Power of Phenol Derivatives. I. Effect of Introducing Alkyl Groups and Halogens, *J. Lab. & Clin. Med.* 19:1216 (Aug.) 1934.

5a. Woodward, Glenn J., Kingery, Lyle B., and Williams, Roger J.: The Fungicidal Power of Phenol Derivatives, II. Strength in the Presence of Proteins, *J. Lab. & Clin. Med.* 20:950 (June) 1935.

6. Peck, Samuel M., and Rosenfeld, Herbert: The Effects of Hydrogen Ion Concentration, Fatty Acids and Vitamin C. on the Growth of Fungi, *J. Invest. Derm.* 1:237-265 (Aug.) 1938.

7. Peck, Samuel M., Rosenfeld, Herbert, Leifer, William, and Bierman, William: Role of Sweat as a Fungicide With Special Reference to the Use of Constituents of Sweat in the Therapy of Fungous Infections, *Arch. Dermat. and Syph.* 39:126 (January) 1939.

7a. Peck, Samuel M., Botvinick, Isadore, and Schwartz, Louis: Dermatophytosis in Industry, *Arch. Dermat. & Syph.* 50:170-178 (Sept.) 1944.

7b. Peck, Samuel M., and Schwartz, Louis: A Practical Plan for Treatment of Superficial Fungus Infections, *Public Health Reports 58*:337-376 (Feb. 26) 1943.

8. Keeney, E., and Broyles, E.: Sodium Propionate in Treatment of Superficial Fungus Infections, *Bull. Johns Hopkins Hosp. 73*:479, 1944.

9. Keeney, E., and Ajello, L.: The Fungistatic and Fungicidal Effect of Sodium Propionate on Common Pathogens, *Bull. Johns Hopkins Hosp. 73*:379, 1943.

10. Keeney, E., Ajello, L., and Lankford, E.: Studies on Common Pathogenic Fungi and on Actinomyces Bovis, *Bull. Johns Hopkins Hosp. 75*:377, 1944.

11. Keeney, E., Ajello, L., Broyles, E., and Lankford, E.: Propionate and Undecylenate Ointments in the Treatment of Tinea Pedis and an *In Vitro* Comparison of their Fungistatic and Anti-Bacterial Effects With Other Ointments, *75*:417, 1944.

12. National Research Council, Conference on Fungus Infection of the Skin, June 20, 1944.

13. Goldman, Leon, Henningsen, A. B., Ringelman, Norbert P., Fox, Harry H., and Hesselbrock, John: Evaluation of a Fungicidal Agent for Fungous Disease of the Feet, *Arch. Dermat. & Syph. 47*:569, 1943.

14. Shapiro, A., and Rothman, S.: Undecylenic Acid in the Treatment of Dermatomycosis, *Arch. Dermat. & Syph. 52*:166, 1945.

15. Hillegas, Arthur B., and Camp, Earl: The Testing of Fungicides Insoluble in Water, *J. Invest. Dermat. 6*:217-226 (June) 1945.

16. Corlett, W. T.: Recent Researches in Ringworm, *J. A. M. A. 32*:589, 1899.

17. Darier, J.: A Text-Book of Dermatology, Philadelphia, Lea & Febiger, 1920.

18. Livingood, Clarence S., and Pillsbury, Donald M.: Ringworm of the Scalp, Prolonged Observation, Family Investigation, Cultural and Immunologic Studies in 130 Cases, *J. Invest. Dermat. 4*:43-57 (February) 1941.

19. Poth, Duncan O., and Kaliski, Sidney R.: Estrogen Therapy of Tinea Capitis, *Arch. Dermat. & Syph. 45*:121-128 (January) 1942.

20. Ringworm of the Scalp Epidemic Stopped, Government Services, *J. A. M. A. 127*:869 (March 31) 1945.

20a. Schwartz, Louis, Peck, Samuel M., Botvinick, Isadore, Leibovitz, Armond Leo, and Frasier, Elizabeth S.: Control of Ringworm of the Scalp Among School Children in Hagerstown, Maryland, 1944-1945, *J. A. M. A. 132*:58-62 (Sept. 14) 1946, and Pub. Health Bull. 294.

21. MacKee, George Miller, Hermann, Franz, and Karp, Florentine, L.: A New Treatment for Anthropophilic Tinea Tonsurans (Microsporon Audouini), *J. Invest. Dermat. 7*:43-52 (Feb.) 1946.

22. Carrick, Lee: Therapy for Tinea Capitis, *J. A. M. A. 131*:1189 (Aug. 10) 1946.

23. Lewis, George M., Hopper, Mary E., and Reiss, Frederick: Ringworm of the Scalp, *J. A. M. A. 132*:62-65 (Sept. 14) 1946.

24. Miller, J. Lowry, Lowenfish, F. Philip, and Beattie, Guila F.: Local Treatment of Tinea Capitis, *J. A. M. A. 132*:67-70 (Sept. 14) 1946.

25. Strickler, Albert: Tinea Capitis, *J. A. M. A. 132*:65-66 (Sept. 14) 1946.

PROGRESS IN ALLERGY THERAPY *

By Samuel M. Feinberg, M. D.**

THE field of allergy is an expansile one. At first concerning itself primarily with hay fever and asthma, it has developed to embrace urticaria, serum and drug reactions, atopic eczema, contact dermatitis, headaches, many gastrointestinal manifestations and the phenomena of some infectious diseases. With proper and intensive investigative approach it promises to unfold as an important factor in many more of the infectious and degenerative diseases. Progress in the therapy of allergy may be discussed along several broad lines.

1. Principle of Sensitization

The principle of sensitivity to a specific substance such as pollen, foods or animal hair, resulting in symptoms of asthma and rhinitis had been described and proven by such pioneers as Blackley, Salter, Floyer and others a hundred and two hundred years ago. But for the most part the teachings of these early prophets went unheeded. It was not until the turn of this century, when the phenomena of induced sensitiveness in animals—anaphylaxis—was being rapidly elaborated that a foundation was laid for a rebirth of interest in related human disease. It was just 40 years ago—in 1906—that Wolff-Eisner (1) called attention to the similarity of human hay fever to the symptoms of sneezing and rubbing of the nose observed in the guinea pig receiving an anaphylactic dose of an antigen. It was in large part due to this similarity of symptoms and on the close resemblance of asthma to the symptoms of bronchospasm in the anaphylactic guinea pig that interest was focused on the importance of applying the knowledge and future developments of anaphylaxis to human manifestations of hypersensitivity.

2. Desensitization

Early in the development of the knowledge of anaphylaxis it was shown that the sensitized animal could be made immune or refractory to shock by the injection of a sublethal dose of the specific agent or

* Presented at the Midyear Meeting of the American Pharmaceutical Manufacturers' Association, December 9, 1946.

** Associate Professor of Medicine and Chief of Division of Allergy, Northwestern University Medical School.

antigen. This process was termed anti-anaphylaxis or desensitization. Around 1910 or 1911 the concept of desensitization began to be applied in human allergy in the treatment of hay fever with pollen extract (2). Later, this procedure was utilized in sensitivity to other antigens, such as animal danders, house dust and fungi. In principle, desensitization in allergy is akin to desensitization in anaphylaxis, but quantitatively the two differ materially. Too frequently the layman or physician gets the impression that as in anaphylactic sensitivity one or two injections given to the allergic patient will desensitize fairly completely and for an extended period. The fact is that desensitization in allergy is a slow tedious process, requiring numerous injections, achieving moderate although usually clinically adequate tolerance, and demonstrating a great tendency for rapid loss of tolerance when injections are discontinued.

Nevertheless, improvements in this process have been developed, by more careful attention to conditions promoting potency and stability of the extracts and by adopting methods of standardization. There is still considerable room for pioneering in improvements in desensitization. We have an apparently correct principle, requiring improved technique and ideas for its perfection. For example, we need antigens that are relatively free from constitutional reactions, requiring a greatly reduced number of injections and at the same time capable of stimulating a greater production of antibodies. We need to devote more time and energy to the study of the mechanism of allergy and desensitization in order to jockey ourselves into the position of possible new approaches.

3. Antigens

Progress has been made in the increasing range of source of allergens. First, the role of pollen was established (3), to be followed by the recognition of the importance of foods, animal epithelium, airborne fungus spores (4) and a number of other inhalant substances. The role of contact allergens was placed on a sound basis as occupational and other hazards. The growing list of new drugs and pharmaceutical products has increased the problem of allergy in that field and has sharpened the interest of the manufacturer and physician. To mention but a few, we have the problem of allergy to such therapeutic products as serums, aspirin, analgesics, local anesthetics, hormones, vitamins, metallic salts, sulfonamides, penicillin and other anti-

biotics, vaccines and the media (such as egg) on which viruses are grown. We have the additional problem of allergy in the worker to many products in the pharmaceutical industry. Here again is a challenge to the pharmaceutical manufacturer to safeguard his product both to the producer and consumer.

The concept of the nature of antigens has undergone evolution. At first thought to be only proteins, later the role of carbohydrates as antigens and as haptens was elaborated. An application of this principle was the despeciation of serum globulin by removing the carbohydrate fraction from it by the aid of an enzyme. The work of Landsteiner (5) and his followers demonstrated that simple chemical substances, although not antigenic in themselves, could be combined with larger molecules, such as proteins, to make them perfect and specific antigens. Thus the concept offered an explanation for the phenomenon of allergy to drugs on the basis that such drugs become conjugated to blood or tissue proteins thus becoming true antigens. Exceptions to the above principle have appeared from time to time. For example, we have been able to demonstrate that some simple chemicals (sulfonechloramides) (6) not only can produce atopic manifestations such as asthma and rhinitis, but also whealing skin reactions and transferable antibodies in man and probably precipitins in the rabbit.

If such simple chemicals, with or without skin reactivity, can produce atopic manifestations, is it too much to imagine that other simple chemicals present in the air from combustion products of coal or from waste products of manufacturing industries may be the source of a large group of unidentified and predominately urban allergy? And perhaps this concept of allergy to simple chemical substances may extend to foods and other possible sources. It is evident that much room for experimentation and progress exists here.

4. Antibodies

The demonstration in 1921 by Prausnitz and Kustner (7) of a passively transferable antibody, the reagin, in human allergy paved the way for a clearer understanding of the mechanism of allergy and for much immunological progress. The allergic (atopic) reaction is due to a union of this antibody with the specific antigen. But since this antibody is not diminished by desensitization, the puzzle of the mechanism of the latter still remained. When Cooke and his asso-

DETROIT PUBLIC LIBRARY

ciates (8), in 1935, demonstrated that in the process of desensitization a new antibody—variously called the blocking, protective or thermostabile antibody—was produced, the principle of immunity through desensitization could be visualized. This antibody blocks the reaction between antigen and reagin. The full role of this immune substance has not yet been established, but it promises to furnish the basis for determination of immunity, it may possibly be produced commercially for passive immunity and it may perhaps be used as a means of aiding the administration of antigens more effectively.

5. Nonspecific Desensitization

From the very beginning of the demonstration of specific desensitization in anaphylaxis and allergy many workers began to turn their attention to the possibility of finding a method which would desensitize or inhibit anaphylaxis or allergy without the use of a specific antigen. By 1932 at least 165 such methods or substances had been reported (9): among these were atropine, ether, chloral hydrate, barium salts, heparin, infection with tubercle bacilli and reduction in barometric pressure. Later some of the additional agents proposed were veronal, avertin, potassium salts, vitamins D, C, and P, hormones, nitrohydrochloric acid and such newspaper headliners as anthallan and ethylene disulfonate. The best that can be said of most of these methods is that although an occasional one possessed a certain degree of merit, for the most part they were either impractical, too hazardous or insufficiently effective.

There are, however, possibilities along the direction of nonspecific agents. For example, X-ray therapy to the chest has been helpful in many chronic cases of asthma. Frequently phenomenal relief from allergy occurs during pregnancy. The remarkable effect of intercurrent infectious disease on the allergic state is an observation familiar to all practicing physicians. An infection accompanied by fever may cause more complete relief of a chronic asthma than painstaking specific treatment. Unfortunately the effect usually is only temporary. Fever therapy by physical agents enabled us to duplicate these results to some degree, but by no means were they comparable to the effect of the actual infection. It seems to me that here is an open invitation for intensive research to isolate and to reproduce the substance or mechanism responsible.

6. Drugs

The discovery of epinephrine and its sympathomimetic action heralded a new era of progress in the symptomatic therapy of allergic manifestations. The isolation of the alkaloid ephedrine and the demonstration of its action when taken orally further advanced this type of therapy. This was followed by the development of a number of related drugs among which may be mentioned racephedrine, benzylphedrine, propadrine, paredrine, neosynephrin, tuamine, privine and others. Whether for topical or systemic effect, the perfect sympathomimetic drug has not yet been made. To produce a drug which will be powerful but selective, yet free from side reactions or compensatory vasodilatation, and to be lasting in its effect is a dream of the chemist and pharmacologist.

Aminophylline is an example of a type of drug owing its antiallergic action to the relaxation of smooth muscle. Other drugs possessing related actions have been presented by pharmaceutical industries, but better antispasmodics are still possible. The iodides are effective in asthma, presumably by stimulating the mucous glands of the bronchi to secrete a thin, non-obstructing secretion. Frequently, however, iodides become objectionable because they produce gastric irritation, acneiform eruptions, swelling of salivary glands and other untoward reactions. It seems to me that it would not be impossible for modern chemists and pharmacologists to find a drug having the desired effect on the mucous glands without the objections of the iodides.

7. Histamine and Antihistaminic Agents

Following the suggestion by Dale and Laidlaw in 1911 that the symptoms of histamine shock resembled those in anaphylaxis, many experimenters added findings tending to substantiate the concept that release of histamine from the tissues is responsible for the anaphylactic reaction. It is true that some of the manifestations of anaphylaxis cannot be explained by histamine effect, but it was argued that histamine is at least the major mechanism. The histamine concept was gradually adopted to explain the allergic reaction in man after Lewis, (11) in 1924, claimed that the histamine effects in man were identical with those of allergy. Many attempts were then made in animals and man to raise the tolerance to histamine by injections of the latter. The preponderance of evidence indicates that a tolerance

to histamine cannot be acquired in that manner. The concept of obtaining such tolerance by the administration of conjugated histamine (histamine-azo-protein or hapamine) has not been satisfactorily established. When Best, (12) in 1929, described the behavior of the enzyme histaminase, hope for an effective antihistaminic substance was entertained. Despite a few enthusiastic reports it has been amply proven that histaminase has no effect on histamine in the living animal (13).

In the last few years a rather intensive search has been going on for an ideal antihistaminic substance. The search has been directed mainly to the type of chemical which is structurally constituted to displace histamine from the cell. The amino acids histidine, cysteine and arginine, first proposed in 1937 (14), were actually such agents, but were entirely too weak in their antihistaminic action and too toxic. In France, Fourneau and his collaborators more than 15 years ago began to synthesize new compounds which displayed antihistaminic and antianaphylactic activity. Their first compounds, however, were too toxic for clinical use.

The more recent histamine antagonists are chemically related and have some degree of clinical value. They are the French compounds:

N′-phenyl-N′-benzyl - N - dimethylethylenediamine (Antergan) (15), N-*p*-methoxybenzyl-N-dimethylaminoethyl - α - aminopyridine (Neoantergan) (16) and the American compounds: β-dimethylaminoethyl benzhydryl ether (Benadryl) (17), N′-pyridyl-N′-benzyl-N-dimethylethylenediamine (Pyribenzamine) (18).

In Europe, Antergan has been replaced by Neoantergan. In an extensive clinical trial with Benadryl and Pyribenzamine and a more limited trial with Neoantergan, we have found these drugs useful symptomatic remedies in allergy (19, 4). They give relief to a large percentage of cases of urticaria, atopic eczema, penicillin and sulfonamide reactions, many cases of hay fever and non-seasonal allergic rhinitis and are of aid in the treatment and prevention of constitutional allergic reactions. In asthma the action of all of these drugs is only slight and does not compare favorably with that of ephedrine or epinephrine. Particularly in allergic rhinitis, Pyribenzamine was the most consistently effective of these three drugs. It is important to remember that all of these drugs are only simple palliative remedies, each dose being effective for only a few hours, that in severe allergic states and in many allergic conditions these drugs may not give even

symptomatic relief, and that with these drugs no tolerance or immunity to allergy is acquired. Specific allergic methods of elimination or desensitization are still essential procedures in allergy.

The antihistaminic drugs have many side reactions. Benadryl is very prone to produce sleepiness, not infrequently so marked that the patient cannot continue the use of the drug. Pyribenzamine possesses a similar action but to a much lesser degree and in a smaller percentage of patients. All these drugs may produce varying degrees of other side reactions, such as gastrointestinal disturbances, dizziness, nervousness, fall in blood pressure, palpitation, mental confusion and excitation.

These drugs have varying degrees of antihistaminic action in animals. Thus, we found that when the different drugs were given to guinea pigs intraperitoneally in the same dose (3 mg. per kilogram) the following number of lethal doses of histamine were required to produce death in all animals: Benadryl, 5; Antergan, 6; Pyribenzamine, 37; and Neoantergan, 125 lethal doses. On the other hand, when 1 lethal dose (LD_{100}) was used with diminishing doses of protective agents, the findings indicated that at these levels no significant differences in the antihistaminic powers of these drugs existed. Anaphylactic death was prevented by small doses of these drugs, and no striking differences between them were noted by decreasing the completely effective concentrations. Studies on histamine and anaphylactic contraction of the guinea-pig intestinal strip indicated a greater discrepancy. For example, a drug showing 7 times the antihistaminic activity of a second drug as measured on the strip showed no greater inhibition of the anaphylactic contraction. We might add also that the anti-allergic activity of these drugs did not parallel their antihistaminic behavior.

There is still room for the manufacturer to develop antihistaminic drugs with more consistent action and less toxic side effects. I know that many phamaceutical houses are vigorously pursuing this plan, for I have been privileged to be designated by several of them as an impartial investigator of their product. But in addition to this, another question should be raised: May not some of the discrepancies between antihistaminic, antianaphylactic and antiallergic potency of these drugs constitute an argument against the generally accepted concept that histamine release is the major explanation of the hypersensitive reaction? The least that can be said is that this relationship must be more thor-

oughly reexamined and that the question of other possible mechanisms of anaphylaxis and allergy must be reopened. In this connection it is my advice to investigators in pharmaceutical industries not to depend solely on antihistaminic action in their quest for effective remedies for allergy. Other screening processes must be invoked.

8. Role of Pharmaceutical Industries

Five to ten million people in this country have recognizable allergic ailments. The field of allergy will ultimately extend to a much greater number when we know more about the allergic processes in infectious and other diseases. What should be the role of the pharmaceutical industries toward helping these millions? It appears to me that industry can have two interests: one, a practical interest in the development of a useful drug or product, and two, an interest in fundamental basic research which may ultimately lead to even broader applications. Among the possible interests of pharmaceutical institutions may be included a study and improvement of antigens, search for new antigens, study of antibodies and their possible therapeutic use, search for a non-specific mechanism or substance, development of new sympathomimetic and other drugs, improvements in antihistaminic substances and a search for drugs which interfere with other steps in the allergic reaction. More basic but less immediately rewarding would be the intensive work along the line of allergy to infection and a serious study of the underlying mechanism of the allergic state or constitution. Much of this work can be done within the confines of the industrial institution and much can be done at properly equipped research centers of universities. Some of the work demands the pooled research efforts of a number of pharmaceutical industries. An example of this is the research required to produce a uniform standard for pollen and other antigens, the lack of which is creating confusion and retarding progress. The Committee on Therapy of the American Academy of Allergy is ready and anxious to cooperate in such and similar undertakings.

Wherever the research is to be done I am sure you will agree that it requires the team work of the pharmaceutical investigator and the experienced observant and research-minded clinician to achieve the best results (20).

REFERENCES

1. Wolff-Eisner, A.: Das Heufieber, sein Wesen und seine Behandlung (Munich: J. F. Lehman, 1906).

2. Noon, L.: Prophylactic Inoculation Against Hay Fever, *Lancet 1*:1572 1911.

3. Blackley, C. H.: Experimentl Researches on the Cause and Treatment of Catarrhus Aestivus (Hay-fever or Hay-asthma) (London: Balliere, Tindall & Cox, 1873).

4. Feinberg, S. M.: Allergy in Practice, 2nd ed. (Chicago: The Year Book Publishers, 1946).

5. Landsteiner, K.: The Specificity of Serological Reactions (Springfield, Ill.: Charles C. Thomas, 1936).

6. Feinberg, S. M., and Watrous, R. M.: Atopy to Simple Chemical Compounds—Sulfonechloramides, *J. Allergy 16*:209, 1945.

7. Prausnitz, C., and Kustner, H.: Studies on Hypersensitiveness, *Zentralbl. f. Bakt. 86*:160, 1921.

8. Cooke, R. A., Barnard, J. H., Hebald S., and Stull, A.: A Mechanism of Protection Produced in Hay-Fever Patients by the Injection of Pollen Extract, *J. Allergy 6*:593, 1935.

9. Hill, H. J., and Martin, L.: A Review of Experimental Studies of Nonspecific Inhibition of Anaphylactic Shock, *Medicine 11*:141, 1932.

10. Dale, H. H., and Laidlaw, P. P.: The Physiological Action of β-iminazolethylamine, *J. Physiol. 41*:318, 1911.

11. Lewis, T., and Grant, R. T.: Vascular Reactions of the Skin to Injury: Notes on the Anaphylactic Skin Reaction, *Heart 13*:219, 1926.

12. Best, C. H.: Disappearance of Histamine From Autolyzing Lung Tissue, *J. Physiol. 67*:256, 1929.

13. Council on Pharmacy and Chemistry: Preliminary Report on Histaminase (Torantil), *J. A. M. A. 115*:1019, 1940.

14. Edblacher, S., Jucker, L., and Baur, H.: Die Beeinflussung der Darmreaktion des Histamine durch Aminosauren, *Ztschr. f. physiol. Chemie 247*:63, 1937.

15. Halpern, B. N.: Les antihistaminiques de synthese. Essais de chimiotherapie des etats allergiques, *Arch. internat. de pharmacodyn. et de therap. 68*:339, 1942.

16. Bovet, D., Hordlois, R., and Watthert, F.: Proprietes antihistaminiques de la N-*p*-methoxybenzyl-N-dimethylaminoethyl-α-aminopyridine, *Compt. rend. Soc. de biol. 138*:99, 1944.

17. Loew, E. R., Kaiser, M. E., and Moore, V.: Synthetic Benzhydryl Alkamine Ethers Effective in Preventing Fatal Experimental Asthma in Guinea Pigs Exposed to Atomized Histamine, *J. Pharmacol. & Exper. Therap. 83*:120, 1945.

18. Mayer, R. L., Huttrer, C. P., and Scholz, C. R.: Antihistaminic and Antianaphylactic Activity of Some α-Pyridino-ethylenediamines, *Science 102*:93, 1945.

19. Feinberg, S. M.: Report to the Council on Pharmacy and Chemistry: Histamine and Anti-Histaminic Agents. Their Experimental and Therapeutic Status, *J. A. M. A. 132*:12, 1946.

20. Feinberg, S. M.: Allergy. Its Present Status and Needs, *Northwestern University Medical School Quarterly Bull., 20*:398, 1946.

THE GENERAL MEDICAL ASPECTS OF ATOMIC ENERGY.*

By Frank H. Krusen, M. D.**

RECENTLY I presided at a medical meeting to discuss the uses and dangers of atomic energy. The medical audience was the most sober and attentive I have ever seen. Obviously all of them were more or less aware of the fearful potentialities of atomic energy and they wanted to learn all they could about it.

The Constructive versus the Destructive Uses of Atomic Energy

We should recognize not only the power of atomic energy to benefit but also its power to destroy mankind. That which has fascinated us most concerning atomic energy is its tremendous potency. If any of you doubt the destructive power of atomic energy and think that the reports on the Hiroshima bombing were "mostly propaganda," you should know these facts. Of the 150 physicians in Hiroshima at the time the atomic bomb fell, sixty-five were killed and most of the rest were so badly injured that they could not treat other injured people. Of 1,780 nurses, 1,654 were dead or too badly hurt to carry on (1). General Grove's figures for the Hiroshima and Nagasaki bombings indicated an average of 68,000 people killed and 90,000 injured per bomb and, according to General Farrell, the bomb at Hiroshima produced "four square miles of absolute destruction and three more of serious damage" (2). In the official report (3) on "Atomic Energy for Military Purposes," H. D. Smyth of Princeton University, Consultant to the Manhattan District, said: "A weapon has been developed that is potentially destructive beyond the wildest nightmares of the imagination. . . . It is conceivable that totally different methods may be discovered for converting matter into energy since it is to be remembered that the energy released in uranium fission corresponds to the utilization of only about 0.1 per cent of its mass. Should a scheme be devised for converting to energy even as

* Read before the meeting of the American Pharmaceutical Manufacturers' Association, December 10, 1946.

** Section on Physical Medicine, Mayo Clinic, Rochester, Minnesota.

much as a few per cent of the matter of some common material, civilization would have the means to commit suicide at will."

This led Yates (4) to remark: "Civilization stands in the twilight zone between a possible Utopia and ultimate destruction . . . Wholesale even planetary death has come to live among us."

Dr. Raymond B. Fosdick (5), president of the Rockefeller Foundation, stated that the search for truth concerning atomic energy "has today brought our civilization to the edge of the abyss, and man is confronted by the tragic irony that when he has been most successful in pushing out the boundaries of knowledge, he has most endangered the possibility of human life on this planet. The pursuit of truth has at last led us to the tools by which we can ourselves become the destroyers of our own institutions and all the bright hopes of the race."

Fear is a strong factor in our concern with atomic energy and we should recognize that we *are* fearful. Fosdick said: "Now we are face to face with this urgent question: Can education and tolerance and understanding and creative intelligence run fast enough to keep us abreast with our own mounting capacity to destroy?"

At the opening session of the United Nations Atomic Energy Commission, Bernard M. Baruch (6) said: "Behind the black portent of the new atomic age, lies a hope which, seized upon with faith, can work our salvation. If we fail, then we have damned every man to be the slave of fear. Let us not deceive ourselves: we must elect world peace or world destruction. Science has torn from nature a secret so vast in its potentialities that our minds cower from the terror it creates. . . . Science, which gave us this dread power, shows that it can be made a giant help to humanity, but science does not show us how to prevent its baleful use . . . Only in the will of mankind lies the answer."

Furthermore, Albert Einstein (7) has commented on the problem of atomic energy: "As Mr. Baruch wisely said, it is a problem not of physics but of ethics. . . . Science has brought forth this danger, but the real problem is in the minds and hearts of men . . . "

Having faced the fact that atomic energy possesses fearful potential dangers, what can we do about it? McGraw (8) sounded the keynote when he said: "We hold in trust a power that is capable of unraveling the very fabric of our civilization. Equally it may be susceptible of development as a mighty force for human welfare. But we

have proved the destructive use while the constructive applications are still in the realm of speculation. At one giant stride our scientific and technological development has so far out-distanced our social engineering, that we have no choice but to turn our full powers of creative imagination to control the forces we have unleashed and to bend them to man's use rather than to his destruction."

This great American Pharmaceutical Manufacturers Association may well stand in the forefront of the ranks which will align themselves in the battle to turn this mighty force from man's destruction to man's benefit.

We are only now making the first feeble efforts in this direction and as was mentioned in the Lilienthal report (9): "We are probably no more able to foresee the ultimate fruits of development than were Faraday's contemporaries to understand what would come of the discovery of electro-magnetic induction."

There are two great fields for beneficial use: "the development of atomic energy as a controlled source of power" (10) and "the application of radiations and radioactivities to the growth of the sciences and practical arts." Atomic scientists believe that "it is probable that the exploitation of atomic energy as a tool for research will outweigh the benefits to be derived from the availability of a new source of power." They think that it would not be astonishing "if the greatest benefit of this program were in fact to lie in therapy for some of the neoplastic diseases, such as cancer, or in the increased understanding of biological systems or of the realities of the physical world, which will in turn open up new fields of human endeavor."

The Governmental Program in Development of Constructive Uses of Atomic Energy

It is perhaps well to know something about the government's plan for the development of research in the medical applications of atomic energy. Your chairman asked specifically that I discuss this point. Actually, although much has been accomplished, no final plans have yet been announced. The governmental developments started with the work of Section S-1 on Atomic Energy of the Office of Scientific Research and Development and continued with the activities of the Manhattan Engineering District Investigating Group. Then there was established the Secretary of War's Interim Committee on Atomic Energy.

Working with this Interim Committee, Manhattan Engineering District has developed excellent plans for making radioactive isotopes available for medical research. This led to the publication of an announcement from the headquarters of the Manhattan project on "Availability of radioactive isotopes" (11). Dr. Paul Aebersold, who speaks today, has been secretary of the committee of scientists attempting to develop a suitable interim mechanism for allocation and distribution of radioactive isotopes.

Supplementing these developments, the office of Mr. Bernard M. Baruch, United States Representative to the United Nations Atomic Energy Commission, with Dr. Richard C. Tolman as scientific adviser, has prepared a number of extremely important reports, including volume 1 on general scientific information; (12) volume 3, a bibliography and check list; (13) and volume 5 on medical uses of atomic energy (14). The final decisions with regard to the government's plan for development of research on the medical aspects of atomic energy will rest with the recently appointed five-man national Atomic Energy Commission under the chairmanship of Mr. David E. Lilienthal.

Fundamental Considerations With Regard to Medical Uses of Atomic Energy

A simple description of some of the recent developments in atomic energy assists one in understanding the general medical aspects. These have been well described by Bacher and Feynman (15). Up until the time of the recent studies on atomic energy, scientists had been able simply to regroup atoms into new patterns. Now the nuclear physicists have discovered ways to transform atoms from one kind to another. This new ability to transmute the elements rather than just to rearrange them permits control over an entirely new group of natural phenomena.

Each atom consists of an electron cloud in the center of which is a heavy nucleus. There are approximately 600 known varieties of atoms. Many have the same kind of electron cloud but possess a different kind of nucleus. Two atoms that have different cores but similar electron clouds are called "isotopes." Different isotopes of a single element are usually distinguished by giving each a number. This number represents the weight of the nucleus. Thus, two hydro-

gen isotopes are known as H-1 and H-2. There are two principal isotopes of natural uranium, U-238 and U-235.

What the nuclear physicists have discovered is a way to change the nucleus of the atom. The new nucleus, however, may not be stable. When the nucleus changes, it may emit gamma rays. An isotope which is capable of changing from one kind to another is called a radioactive isotope. Since radioactivity can easily be detected with modern instruments, radioactive isotopes can readily be located among stable atoms. This ability to detect the presence of radioactive isotopes is of tremendous value in the solution of many biologic and chemical problems. Radioactive isotopes can be used in medicine and in scientific research as tracer elements.

Nichols and Ruhoff (16) have said that one of the most important by-products of the development of the atomic bomb is the fact that there are now available a host of new tools for basic research in many fields including medicine, chemistry and physics. New radioactive materials can be produced synthetically in a pile. Also, there have been produced new radioactive fission materials, new chemical and physical processes and new mathematical technics. In the sum total of their application, these new technical and engineering methods may be of greater value than the power potentialities of atomic energy.

Cohn (17) said that most of the radioactive species produced in a pile can also be made in a cyclotron. A few species appear in fission, however, which can not be made conveniently otherwise. The combined use of the pile and the cyclotron has brought the present list of radioactive isotopes to about 450. The important contribution of the pile is that it can make certain radioisotopes available in tremendous quantities.

By virtue of their radioactivity, radioisotopes can be detected at a distance from themselves. Therefore samples need not be purified to the extent necessary for ordinary physical or chemical analyses. Furthermore, the fact that each radioisotope has its own specific and unique type of radiation permits exact identification.

Of particular significance in medicine is the fact that the radiation from radioactive iodine extends outside of the human body and its approximate location can be detected by placing instruments on the surface of the body. For example, in studying the effect of radioiodine on the thyroid gland, the rate at which it enters and leaves the gland can be followed continuously. Such studies were impossible

before the manufacture of radioactive iodine. Once the proper information was available, it led to a method of utilizing larger amounts of radioactive iodine in treatment for hyperthyroidism.

It has been stressed by Allison, who addresses you today, and by Cohn that there are tremendous possibilities in the utilization of radioactive carbon because among the many atomic species which make up living matter carbon occupies a unique position owing to the enormous number of compounds it can form. Cohn voiced the opinion that it is possible that discoveries made in researches with the carbon isotope C-14 may be as important and far-reaching as the discovery of fission itself.

Therapeutic Applications of Atomic Energy

Rhoads and Solomon (18) stated that to date only two artificial radioactive isotopes have been proved conclusively to be of therapeutic value. These are phosphorus-32 with a half life of 14.3 days, and iodine-130 and iodine-131, with half lives of 12.6 hours and 8.0 days, respectively. Until recently, only limited quantities of these two isotopes have been available from the costly and time-consuming cyclotron bombardment. Now, existing piles can provide amounts of these isotopes which will be adequate for medical needs.

Of the disorders which can be treated effectively with P-32, polycythemia alone has been controlled for long periods. In leukemia, there is some evidence that treatment with P-32 results in fewer undesirable side effects than occur when roentgen rays are employed in therapy but there is no greater prolongation of life. Radioactive iodine is notably successful at present only in the treatment for hyperthyroidism. Cancer of the thyroid gland, on the other hand, has not been cured by treatment with radioactive iodine, though a noticeable palliative effect is apparent in a very few cases.

Hall and his associates at the Mayo Clinic have employed radioactive phosphorus as a therapeutic agent since 1941. The most favorable results have been observed in polycythemia vera. Of 103 patients treated to date, 80 per cent obtained satisfactory remissions lasting from five months to four years. Partial remissions were obtained in the remaining 20 per cent. With recurrence of the polycythemia months or years later, remissions were induced a second time following subsequent treatment with the isotope. In the chronic

forms of leukemia, remissions similar to those observed following roentgen therapy were induced with radioactive phosphorus.

Rhoads and Solomon mentioned significantly that "the very fact that two forms of cancer, leukemia with its allied disorders, and thyroid cancer are now treated with radioactive isotopes suggests, however, that other types of neoplastic disease may be found to be susceptible in the future. In particular, the synthesis of radioactive elements into compounds which already have a demonstrable physiological effect on neoplastic disease must be explored." They added that it was easy to imagine that radioactive isotopes might be provided as a simple substitute for roentgen rays in photography and thought that it might be possible in remote parts of the world where conventional X-ray apparatus is not available, to provide a safe, simple and inexpensive method of taking ordinary X-ray films.

At the Mayo Foundation, Higgins, Larson and Keating have conducted studies dealing with various phases of the employment of radio-iodine in the diagnosis and treatment of thyroid disease. These studies have thrown considerable light on the manner and rate by which inorganic iodine is converted into di-iodotyrosine and thyroxin. The method has been and is receiving extensive use in investigating the relationship between the thyroid gland and the anterior hypophysis. It has been the definitive tool for showing the mode of action of thiouracil and other thyroid inhibitors.

Radioactive iodine appears to have a definite place in the treatment of exophthalmic goiter, at least in certain selected cases. These will probably include patients for whom thyroidectomy represents an excessive risk, either by reason of the seriousness of the hyperthyroidism or because of the existence of serious complicating conditions such as heart disease. It may prove to be the method of choice for treatment of patients whose hyperthyroidism has recurred after thyroidectomy. In this latter group, results obtained with thiouracil have been particularly disappointing.

The Employment of Atomic Energy in Medical Research

Greatest emphasis should probably be placed on the promise afforded by the use of isotopes as tracers in the fields of pure chemistry and biologic and medical chemistry. The value of these new tools for acquiring information has so broadened the fields of chemistry

and physiology that one can anticipate almost limitless advances. Certainly the ability to investigate the dynamic equilibrium of chemical and biologic processes has brought us to a new frontier. At the Mayo Foundation, Bollman has employed radioactive phosphorus in the study of the metabolism of resting and exercising muscles, the permeability of muscle during shock and many problems of phospholipid metabolism. He was in agreement with the editorial in the Bulletin of the Atomic Scientists which stated (19): "The most significant uses of artificial radioactive materials will be in laboratory researches in which the tagging of atoms through their radiations will enable technical advances to be made whose very nature cannot be predicted at this time."

The Deleterious Effects of Atomic Energy

Finally, from the general medical standpoint, all physicians will be interested in the possible deleterious effects of atomic energy on human beings. Since Warren will discuss "Physiologic reactions to radioactive isotopes," I shall touch on only one phase of this subject. It was my privilege recently to hear Sir Lionel Whitby (20), Hematologic Consultant to the British Atomic Energy Station at Didcot, talk on "The hematological effects of radiation." He said, "The effect of various radioactive substances on the living organism has become a matter of universal importance and of interest to every living being since the crucial decision was made to use atomic energy for warlike purposes." He added that it must be borne in mind that nuclear physicists are now working with rays or ionizing particles the exact capacity of which for damage is quite unknown. Such irradiations influence cytochemistry, chromosome development and gene mutation. In examinations of the blood, at least as much significance should be attached to the appearance of any bizarre or unusual white corpuscles as to the more commonly reported changes in their total number. All experimental evidence to date suggests that the damaging effects of radiation are exerted on the young, dividing cells rather than on the mature cells which are circulating. Damage at an early stage, if it does not kill the cell, may render it incapable of complete maturation. It is generally considered that the lymphocyte is the most radiosensitive cell, because reduction of number of lymphocytes is the earliest, the most marked and the most consistent blood change induced by therapeutic doses, but lymphocytes are able to re-

cover rapidly. Whitby remarked that nuclear physicists are notoriously careless about their own protection and most of them are only vaguely aware of the hazards of their occupation—an observation I have heard made by two of my fellow speakers, Allison and Warren. Whitby also described briefly the effects of radiation on the reproductive system. In the male the gonads may be affected and spermatogenesis may be stopped. Even complete atrophy of the seminiferous tubules has been observed in some cases. In the female miscarriages may occur. Insidious chromosome and gene mutations may be produced which may affect progeny for several generations.

Conclusions

I may conclude by reiterating that our nuclear scientists have unleashed a mighty power for evil or for good and that we must exert every effort to make certain that the potentialities for good are those which are developed. Already in the field of medicine we have a number of promising leads for utilization of atomic energy in therapy and even brighter vistas open before us in the field of medical research. Perhaps this association will be in a position to exert leadership in diversion of the enormous forces of atomic energy from warlike to peaceful scientific pursuits, for, as Fosdick has said, this is "the mighty imperative of our time."

In closing, I should like to read the appropriate verses on "Atomic Power" (21) by Thomson King.

Before recorded history began
Prometheus, symbol of Science, brought us fire,
The altar and the hearth were our desire;
On these were built the faith and hope of man.
Then wood and stone and bronze and steel and steam
In turn became the servants of our will;
Knowledge we got and with it thought to fill

Each need and want, to realize each dream.
Again Prometheus brings a magic gift,
Which scarce we know if we should ban or bless.
The boldest hesitate, the fearful cower,
Before this weapon, deadly, sure and swift.
Amazed we stand, appalled at our success;
For who are we to wield this cosmic power?

REFERENCES

1. Hersey, John: Hiroshima. New York, Alfred A. Knopf, Inc., 1946, 118 pp.

2. Solomon, A. K., and Morrison, Philip: The military effectiveness of the atomic bomb. In: Scientific information transmitted to the United Nations Atomic Energy Commission by the United States Representative. New York, prepared in the office of Bernard M. Baruch (June 14) 1946, vol. 1, pp. 35-42.

3. Smyth, H. D.: Atomic energy for military purposes; the official report on the development of the atomic bomb under the auspices of the United States Government, 1940-1945. Princeton University Press, 1946, 308 pp.

4. Yates, R. F.: Atom smashers; a story of discovery. New York, Didier, 1945, 182 pp.

5. Fosdick, R. D.: The Rockefeller Foundation; a review for 1945. New York, privately printed, 1946, 63 pp.

6. Baruch, B. M.: Opening address before the Atomic Energy Commission of the United Nations. New York Times (June 15) 1946.

7. Einstein, Albert: The real problem is in the hearts of men. New York Times Magazine (June 23) 1946, pp. 7, 42-44.

8. McGraw, J. H., Jr.: The atom: new source of energy; a tide in the affairs of men. New York, McGraw-Hill Publishing Company, 1945, 6 pp.

9. A report on the international control of atomic energy. Department of State Publication No. 2498. Washington, D. C., U. S. Government Printing Office (Mar. 16) 1946, 61 pp.

10. Compton, A. H., Fermi, E., Lawrence, E. O., and Oppenheimer, J. R.: Quoted in: A report on the international control of atomic energy.

11. Announcement from headquarters of the Manhattan Project: Availability of radioactive isotopes. *Science 103*:697 (June 14) 1946.

12. Scientific information transmitted to the United Nations Atomic Energy Commission by the United States Representative. New York, prepared by the office of Bernard M. Baruch (June 14) 1946, vol. 1, 71 pp.

13. Scientific information transmitted to the United Nations Atomic Energy Commission by the United States Representative; bibliography and check list. New York, prepared by the office of Bernard M. Baruch (Aug. 15) 1946, vol. 3, 25 pp.

14. Rhoads, C. P.: Medical uses of atomic energy. In: Scientific information transmitted to the United Nations Atomic Energy Commission by the United States Representative. New York, prepared by the office of Bernard M. Baruch (Sept. 23) 1946, vol. 5, pp. 1-12.

15. Bacher, R. F., and Feynman, R. P.: Introduction to atomic energy. In: Scientific information transmitted to the United Nations Atomic Energy Commission by the United States Representative. New York, prepared by the office of Bernard M. Baruch (June 14) 1946, vol. 1, pp. 1-19.

16. Nichols, K. D., and Ruhoff, J. R.: Production and utilization of uranium-235 and plutonium-239. In: Scientific information transmitted to the United Nations Atomic Energy Commission by the United States Representative. New York, prepared by the office of Bernard M. Baruch (June 14) 1946, vol. 1, pp. 20-33.

17. Cohn, W. E.: Radioisotopes in basic and applied research. In: Scientific information transmitted to the United Nations Atomic Energy Commission by the United States Representative. New York, prepared by the office of Bernard M. Baruch (June 14) 1946, vol. 1, pp. 43-51.

18. Rhoads, C. P., and Solomon, A. K.: Therapeutic uses of artificial radioactivity. In: Scientific information transmitted to the United States Atomic Energy Commission by the United States Representative. New York, prepared by the office of Bernard M. Baruch (June 14) 1946, vol. 1, pp. 52-60.

19. Editorial: Medical and industrial uses of pile products. *Bull. Atomic Scientists* 1:1, 16-17 (Apr. 15) 1946.

20. Whitby, Lionel: Hematological effects of radiation. Mayo Foundation Lecture. Unpublished data.

21. King, Thomson: Atomic power (verse). *Scientific Monthly* 63:248 (Oct.) 1946.

SELECTED ABSTRACTS

The Cough Syrup. E. M. Boyd. *Brit. Med. J.* No. 4480, 735 (1946). Studies of the antitussive action of Syrup B. P. in a group of 28 persons led to the conclusion that the complete relief experienced by 68 per cent was due to a soothing action on the irritated pharynx and upper respiratory tract.

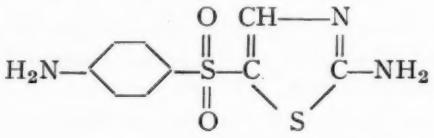
Additional studies were undertaken on rabbits, cats and guinea pigs to determine whether syrups alone exert a true expectorant action. Boyd *et al.* have investigated the subject of expectorants extensively since 1941, and have developed a method for measuring the output of respiratory-tract fluid (R. T. F.) This technic involves collecting R. T. F. through a T-cannula ligated into the trachea of lightly anesthetized or decerebrate animals, with the inhaled air warmed to body temperature and saturated with water vapor. Through use of this procedure, the author and various collaborators have studied the effect upon the output and composition of R. T. F. of a number of drugs.

In the present investigation, the effect of the following B. P. syrups was studied: Simple Syrup and Syrups of Wild Cherry, Squill, Licorice, Tolu, and Ginger. It was found that the syrup vehicle of a cough syrup exerts a short demulcent effect upon the irritated mucosa of the pharynx and upper respiratory tract. The syrup which entered the stomach had little or no expectorant effect in itself, in that it did not increase the output of R. T. F. Expectorant drugs added to the syrup began to increase the output of R. T. F. at about the time that the local antitussive effect of the syrup alone had begun to wear off.

It is felt that the observations made in this study offer an explanation of the action of expectorants as used in cough syrups, as well as justifying their continued use in such medication.

Promizole Treatment of Leprosy: A Preliminary Report. G. H. Faget, R. C. Pogge and F. A. Johansen. *Pub. Health Rep. 61,* 957 (1946). The therapeutic results obtained in the treatment of a small number of cases of leprosy with promizole were sufficiently encouraging to warrant further clinical study of this drug.

Promizole was synthesized by Parke Davis and Co. for the treatment of mycobacterial diseases. It is 2, 4′-diamino-5-thiasolylphenyl sulfone, and has the following structure:



Preliminary clinical trial of promizole in experimental and clinical tuberculosis failed to yield promising results except in cases of tuberculosis of the skin. It was found to be relatively nontoxic when administered by mouth, and the similarity of its structure to those of promin and diasone suggested that it merited clinical trial in the treatment of leprosy.

Brief case reports are presented on seven patients who received promizole treatment for approximately one year. In all of these cases skin smears were positive for *Mycobacterium leprae* at the start of the treatment. In two other cases promizole treatment was discontinued because of general malaise and repeated febrile reactions, respectively.

The initial dosage was 0.5 gm. three times daily, the level later being raised to 2 gm. three times daily. All patients in the group of seven tolerated the drug well.

Clinical improvement was occasionally observed in a shorter time than could be demonstrated with promin or diasone. In only one case, however, were skin smears found to be negative for *M. leprae* after one year of treatment with promizole.

Studies are being continued on the seven cases described in the paper, and on eight additional patients.

Present Status of Diasone in the Treatment of Leprosy: Brief Clinical Note. G. H. Faget, R. C. Pogge and F. A. Johansen. *Pub. Health Rep. 61,* 960 (1946). The report summarizes the present status of 104 patients who received diasone orally in the treatment of leprosy. Diasone (Abbott) is disodium formaldehyde sulfoxylate diamino diphenyl sulfone; in contrast to promin which, because of its toxicity by mouth, is usually administered intravenously, diasone is well tolerated when given orally.

The daily initial dose for adults was usually 0.33 gm. for the first two weeks, being gradually increased to 1.00 gm. For children, the daily dose varied from 0.17 gm. to 0.5 gm.

The authors state that a period of six months appears to be necessary for changes in the specific lesions to become apparent under diasone treatment. Sixty-six of the 104 patients received treatment for six months or longer. Among this group, there was objective improvement in the specific leprous lesions in 65 per cent of the cases, and in 12 per cent there were changes in various nonspecific infections. No demonstrable change was observed in the remaining 23 per cent.

Skin-scrapings of 24 per cent of the diasone-treated patients were found to be negative for *Mycobacterium leprae*. This finding is stated to compare favorably with the results achieved by the intravenous administration of promin.

In 25 cases diasone treatment was discontinued because of various drug reactions such as increased erythema nodosum, dermatitis, gastric intolerance, hematuria, anemia, and others. Six additional patients absconded from the institution.

Four brief case reports are presented as typical of a larger group.

Instructions for Using ANTU as a Poison for the Common Norway Rat. C. P. Richter and J. T. Emlen, Jr. *Pub. Health Rep. 61,* 602 (1946). The instructions presented for the use of ANTU (alpha-naphthyl thiourea) in the control of rats are based upon the experience gained in a three-year test in Baltimore, Md., and also through its use by the U. S. Fish and Wildlife Service, the U. S. Public Health Service, and several professional exterminator companies. In Baltimore the rat population was reduced 90 per cent or more, and no human beings were poisoned.

ANTU occurs as a fine, bluish-gray powder having a particle size of 20-100 μ. It is highly insoluble in water, has no perceptible odor and only a transient bitter taste. It is stable to heat, and is believed to undergo little if any deterioration during several years of dry storage. It mixes evenly with all kinds of food or ground grain, and adheres readily to dry or wet foods when applied as a dust. Similarly it adheres to the feet and hair of rats which run through areas dusted with it, and thus the animals ingest the chemical by licking it from their bodies.

The efficacy of ANTU depends upon the ingestion of a fatal, single dose, since a sublethal dose produces a tolerance which lasts about thirty days, together with an aversion which may last for several months. The poison acts chiefly upon the lungs. Within a few hours after the ingestion of a fatal dose, the lungs and thoracic cavity become filled; the animal drowns in its own secretions. Usually the difficulty of breathing drives the rat out-of-doors, death occurring in from ten to twenty-four hours.

ANTU is a highly specific poison for the Norway rat, which is the type commonly found in both urban and rural areas in this and most other countries. It is much less effective against roof or Alexandrine rats and house mice. It does not poison chickens, pigeons, rabbits, squirrels or guinea pigs. It is not usually fatal to dogs or cats, since these animals ordinarily vomit before the poison has been absorbed. It is believed that ANTU is probably nontoxic to man except in large doses.

ANTU may be mixed with or dusted on ground baits, such as grain or yellow corn, in a 2 or 3 per cent concentration. A 50 per cent mixture of the chemical in flour may be dusted on the floors and runways and also pumped into the openings of burrows with a dust sprayer such as is used for some insecticides. A 1 or 2 per cent suspension of the poison in water may also be placed in shallow dishes.

It is recommended that a rat-control campaign should include at least an entire block in urban areas, or all of the buildings on a farm. Sufficient baits to poison all of the rats at one time should be used. Pre-baiting with unpoisoned baits for several days may be necessary in order to ascertain that the animals will eat the bait freely. No other sources of food or water should be available.

Use of "Benadryl" for Penicillin Urticaria: Preliminary Report. R. R. Willcox. *Brit. Med. J.* No. 4480, 732 (1946). Six cases of urticaria were treated with benadryl (β-dimethylaminoethyl benzhydryl ether hydrochloride) in doses totaling from 150 to 450 mg. In five of the cases the urticaria was associated with intramuscular penicillin therapy, and benadryl was successful in controlling the drug reaction in four patients.

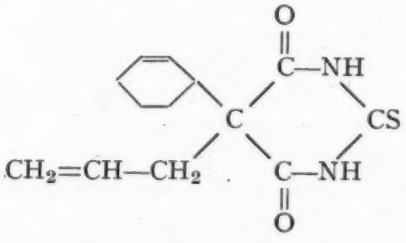
In the sixth case, the diagnosis was giant urticaria and drug sensitivity. There was no history of previous allergy or sulfonamide

administration. Following the administration of adrenalin and ephedrine, a course of sulfathiazole was instituted, but the latter was discontinued when a severe reaction soon developed. Although the patient responded well to benadryl, he later experienced a relapse after the drug was discontinued, and it was necessary to administer a second course of treatment.

In the single case in which failure was noted with benadryl therapy, the patient received adrenalin concurrently. Both drugs were discontinued after a severe reaction had developed. The case was thereafter treated successfully with ephedrine. This patient had received 2,400,000 units of penicillin in conjunction with ten daily intravenous injections of 60 mg. of mapharsen for the treatment of primary syphilis.

Kemithal: A New Intravenous Anesthetic. H. C. Carrington and J. Raventós. *Brit. J. Pharmacol. Therapy 1,* 215 (1946). The pharmacology of kemithal was investigated on mice, monkeys, dogs and rabbits, comparison being made with evipan (Hexobarbitone B. P.) and pentothal.

Kemithal is 5-$\triangle^{2:3}$-cyclohexenyl-5-allyl-2-thiobarbituric acid. The free acid melts at 142° C. and is sparingly soluble in water but readily soluble in most organic solvents. It has the following structure:



Its sodium salt is a pale yellow, slightly hygroscopic powder which is stable in the absence of air. It is soluble in water to the extent of 20 per cent. A 10 per cent solution has a pH of 10.6; evipan and pentothal solutions have a pH of 11.5 and 10.6, respectively. Solutions of the sodium salt of kemithal are stable for four to five hours.

Administered intravenously to mice, monkeys and dogs, kemithal had about one-half the anesthetic potency, weight for weight, as

pentothal, and slightly less than hexobarbitone. In mice its therapeutic ratio was considerably greater than that of the other two drugs. The duration of action of equiactive anesthetic doses of the three drugs was about the same. Determination of the concentrations of kemithal and pentothal in the blood at different levels of anesthesia suggested that kemithal anesthesia can be obtained with less danger of respiratory arrest.

The rate at which kemithal and hexobarbitone disappear from the blood was studied in rabbits. Kemithal is almost completely destroyed in the body. Not more than 5 per cent of the unchanged material and substances giving a positive test for barbituric acid could be recovered from the urine of rabbits during three days; most of this appeared within twenty-four hours. Studies of the changes in the blood levels of kemithal in men under anesthesia and of its excretion in the urine yielded results essentially the same as those observed in rabbits.

No histological changes were found in the tissues of rabbits which received 50 mg. of kemithal intravenously daily for two weeks.

The Similarity of the Effect of Podophyllin and Colchicine and Their Use in the Treatment of Condylomata Acuminata. L. S. King and M. Sullivan. *Science 104,* 244 (1946). Although satisfactory clinical results have been obtained in the treatment of condylomata acuminata by topical applications of podophyllin in oil, its mode of action has not been previously described.

The application of podophyllin to normal rabbit and human skin was found to produce unusual changes affecting the epidermis. Altered cells, designated as "podophyllin cells," were found to result from such treatment of both normal skin and condylomata. There was an alteration of nuclear pattern, a breakup of chromatin masses into distorted mitotic figures principally but not entirely of the metaphase, and other changes.

Colchicine suspensions in oil applied to rabbit skin produced pathologic changes identical with those brought about by podophyllin, but more intense and of shorter duration.

The fact that podophyllin and colchicine exhibit little effect when applied to verrucae vulgares or other lesions with extensive keratinization suggests that the penetrating power of the drugs is slight.

BOOK REVIEWS

English-French and French-English Technical Dictionary. By Francis Cusset. 590 pages. Chemical Publishing Co., Inc., New York, 1946. Price: $5.00.

According to the title page, this dictionary is intended to include the terminology used in "metallurgy, mining, electricity, chemistry, mechanics and science." Even a casual inspection of the book immediately reveals that it is predominately devoted to fields other than chemistry. It appears that the specific fields mentioned, other than chemistry, have been adequately covered, although the all-inclusive term "science" might well be omitted from the enumeration of the branches of learning embraced.

The paucity of common chemical terms contained in this volume may be illustrated by the fact that the following words, selected at random for the purpose of checking, are lacking: *alcaloïde* (alkaloid), *mannite* (mannitol), *fiole* (flask), *ballon* (round-bottomed flask), *bain-marie* (water bath), *becherglas* (beaker), and *chloroforme* (chloroform).

There is a lack of uniformity in spelling; e. g., on page 7 will be found "acid (sulfuric)" and on page 247 "sulphate," "sulphide," "sulphide" and "sulphur."

The English-French section of the dictionary is contained on pages 5-282; the French-English translation occupies pages 283-551. A supplementary list, both English-French and French-English, is provided on pages 553-581.

An appendix includes tables of equivalents of metric and English units of linear measurement, area, volume, weight, pressure, specific weight, power, etc. Methods of calculation for thermometry and the conversion of quantities of heat are given. A table of monetary equivalents is also presented.

It is doubtful whether the chemist will find this dictionary complete enough for his purpose, although the engineer may find it useful.

A. A. Dodge

Concise Chemical and Technical Dictionary. By H. Bennett. xxxix + 1055 pages. Chemical Publishing Co., Brooklyn, N. Y., 1947. Price, $10.00.

The editor has attempted to compile a dictionary of sufficient scope to prove of value to those who wish to find the meaning of technical and chemical terms. An introductory chapter discusses briefly the nomenclature of organic compounds which is a help to those lacking in a fundamental knowledge of organic chemistry. An alphabetical list of organic radicals with their formulas is also included. The pronunciation of chemical words based on a report of the Nomenclature, Spelling and Pronunciation Committee of the American Chemical Society (previously published in the *J. Ind. & Eng. Chem. News Ed. 12,* 202 (1934) is also a useful reference.

As to the chemical and technical words covered over 50,000 are included. They range from purely chemical terms and names to those in the field of physics, engineering and the biological sciences. A number of trade names of proprietary products are also incorporated particularly those in the editor's field of specialization: emulsions, waxes, oils, etc.

It is difficult to assess the completeness of scope in such a dictionary but it is obviously impossible to cover in a single volume all of the technical terms embraced in all fields of science. Those terms and names that are included seem fairly accurate but the perfect work in this category never has and never will be accomplished. One of the real difficulties has been in giving such a brief definition of some terms the editor has given only part truths or very narrow interpretations of the meaning. Possibly this could not be avoided without the use of several volumes of an encyclopedic nature rather than in 1000 pages.

The Chemical and Technical Dictionary is a useful reference but it must not be taken as authoritative or as an exhaustive and complete treatise. Pharmacists, particularly those in manufacturing and research, will find a place for it with their reference books but its limitations must not be overlooked.

L. F. Tice

The Preservation of Proteins by Drying, with Special Reference to the Production of Dried Human Serum and Plasma for Transfusion. By R. I. N. Greaves, M. D., Medical Research Council. Special Report Series No. 258 His Majesty's Stationery Office, London, 1946. Price, *2s.*, *od.* net. (British Information Services, 30 Rockefeller Plaza, New York 20, N. Y.).

This is a paper bound illustrated report of the development and the use of the "freeze drying" method for serum and plasma during the war in England. Those in the United States who use similar methods for drying highly labile materials will find this publication of interest and a worthwhile addition to their list of references on the subject.

L. F. Tice

The Cultivation of Viruses and Rickettsiae in the Chick Embryo. By W. I. B. Beveridge and F. M. Burnet. Medical Research Council Special Report Series No. 256 His Majesty's Stationery Office, London, 1946. Price, *2s.*, *od.* net. (British Information Services, 30 Rockefeller Plaza, New York 20, N. Y.).

This report is a successor to a previous monograph by Burnet in 1936.

A great deal of progress has been made in this highly significant technic in the past decade and this method is now the classic one for the cultivation of viruses. All those workers in this field as well as bacteriologists and immunologists will find this publication very valuable and quite thoroughly done with diagrams and illustrations.

L. F. Tice

one of the oldest
and most reliable
Protections
against
Infection

For cuts, abrasions and minor wounds
Official 2%

IODINE

PREPARATIONS

MILD TINCTURE OF IODINE U.S.P. XII

Mild Tincture of Iodine may be prepared as follows:

Iodine	20 Gm.
Sodium Iodide	24 Gm.
Diluted Alcohol, a sufficient quantity, to make	1000 cc.

Dissolve the iodine and sodium iodide in a sufficient quantity of diluted alcohol to make product measure 1000 cc.

SOLUTION OF IODINE U.S.P. XII

Iodine	20 Gm.
Sodium Iodide	24 Gm.
Distilled Water, a sufficient quantity, to make	1000 cc.

Dissolve the iodine and sodium iodide in 50 cc. of distilled water, then add sufficient distilled water to make the product measure 1000 cc.

Iodine
Educational Bureau, Inc.

120 Broadway, New York 5, N.Y.

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

Manuscripts should be sent to the Editor, who does not assume any responsibility in connection with the views or investigations of contributors of accepted manuscripts, other than to exercise general care in selection.

Contributors are allowed a reasonable number of copies of this Journal, free of charge, if applied for when the proof is returned.

Reprints, if desired, should be ordered when the proof is returned. The table below shows the *approximate* cost of reprints, the make-up of the pages to be identically the same as in the Journal. The actual cost may vary from the figures given, and will depend upon the amount of presswork, paper, binding, and other factors. Reprints containing half-tones may be expected to cost somewhat more than the rates given.

	2 pp.	4 pp.	8 pp.	16 pp.	Covers with Titles
50 copies	$3.50	$6.00	$10.50	$11.25	50 copies .....$ 5.00
100 "	4.25	7.00	14.00	15.00	100 " 6.50
250 "	5.25	9.00	18.75	20.00	250 " 10.25

The American Red Cross
Carries on
Give!